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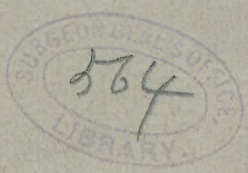
BY

SIMON FLEXNER



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A STATISTICAL AND EXPERIMENTAL STUDY OF TERMINAL INFECTIONS.*

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The recognition of the part played by bacterial infection in the causation of death in chronic diseases has gained in importance with the multiplication of observations upon the occurrence of such infections in human beings, the subjects of chronic diseases of the heart, kidney, liver, and other organs. The data for a proper appreciation of the relation existing between bacterial infection and chronic disease are to be gained less by the clinical observation of cases than by systematic bacteriological examinations at autopsies. The routine study of cases at autopsy by bacteriological methods will not infrequently reveal the presence of pathogenic micro-organisms which were, perhaps, unsuspected during the life of the patient. This fact has been demonstrated repeatedly in the course of the autopsy work at the Johns Hopkins Hospital, where for some time past it has been the practice to make routine bacteriological examinations. Indeed, such examinations have come to be regarded as belonging to the technique of the post-mortem examination. The data which the first part of this paper embodies are taken from the pathological records of the hospital, and represent the results of bacteriological examinations made by Drs. Welch, Councilman, Barker, Blumer, Livingood, and myself.

The routine bacteriological examination of ordinary cases is readily made and does not take much time, while the investigation of general, multiple, and mixed infections requires much time and patience. The proper study of cases demands the preparation of cul-

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tures from the various cavities and all the viscera of the body, and this is equally true whether a definite local infectious process is discovered or not. The distribution of bacteria is not always a regular one, and with a given local inflammatory process of bacterial origin secondary bacterial accumulations may be present in some organs and absent from others. Where no such special localization occurs only a complete set of cultures can be taken to exclude the possibility of bacterial development.

Negative results in bacteriological examinations do not necessarily afford positive proof of the absence of micro-organisms, as these may have been present in such small numbers as to escape detection, or have been irregularly distributed in an organ, or at the time of examination have been dead; or, finally, the culture media upon which they have been transplanted may not have been suitable to their growth. In view of some of these possibilities, cover-slip preparations from organs and exudates should be made and examined along with the study of cultures.

Out of the 793 autopsies performed in the Johns Hopkins Hospital I have found in the records 255 in which occurred chronic heart or kidney disease, or both combined, and in which the bacteriological examination was sufficiently complete to make them of use for this paper. This number does not represent all the cases of chronic heart and kidney disease that came to autopsy. In some the bacteriological examination was either not carried out at all or the records do not suffice for our purpose. Tubercular infection is not included in this summary, although we are not unmindful of the occurrence of acute miliary tuberculosis as a terminal event in cases with some focus of localized tuberculosis. Of the 255 cases mentioned, 213 gave positive and 42 negative results.

If we direct our attention to the results of the study by bacteriological means of cases of chronic Bright's disease, in which the kidney lesions were the chief feature, we find that of 32 cases unassociated with cardiac or other chronic disease, 29 gave positive and 3 negative results. Similarly of 112 cases of combined chronic renal and chronic cardiac disease, 85 yielded positive and 27 negative re-

sults. In a considerable number of cases of chronic Bright's disease other chronic diseases were present. These consisted of tumours, such as carcinomata, sarcomata, and myomata, of cirrhosis of the liver and lungs, chronic proliferative peritonitis, etc. Of 54 cases of combined chronic Bright's disease, bacteriological examination gave 51 positive and 3 negative results.

A similar study of the cases of chronic heart disease yields the following:

The number of cases of heart disease alone in which bacteriological examinations were made was 41, of which 32 were positive and 9 negative. The number of cases of chronic heart disease associated with other chronic diseases than chronic Bright's disease was 22, of which 16 gave positive and 6 negative results. The cases of combined chronic heart and kidney diseases are the same as are given with the summary relating to the latter organ.

For the purpose of this paper no attempt was made to separate the primary heart from the primary kidney cases where both organs were affected. Again, the cardio-vascular system has been regarded as a whole, no division having been made into primary arterial and primary cardiac disease, provided that the heart was the seat of pathological changes. These latter consisted of hypertrophy with and without dilatation, disease of the coronary arteries, fibrous myocarditis, and chronic adhesive pericarditis.

The infections may be local or general. The former are much more common than the latter, and are found in a large proportion of all cases of chronic Bright's disease, arterio-sclerosis, cirrhosis of the liver, and other chronic diseases. Affections of the serous membranes (acute peritonitis, pleuritis, and pericarditis), meninges, and endocardium are the most frequent, but not the only lesions. Special localizations of the micro-organisms are met with in the viscera.

We shall first consider the general infections. No special group of bacteria is present in these in contradistinction to those present in the local infections. Not infrequently a local lesion, such as erysipelas, acute peritonitis, or acute endocarditis, exists which antedates the general invasion of the body by the infectious agent. It, how-

ever, may and actually does happen that the point of entrance of the micro-organisms can not be made out at the autopsy. Either no lesion exists at the place of entrance or, as is more probable, it is so small and insignificant as to escape detection. Among the cases of general infection are found examples of cryptogenetic infection, in which the primary focus is so hidden that it is found at autopsy only after painstaking search.*

In the series of chronic kidney diseases are included 38 cases of general infection: namely, Bright's disease alone, 3 (out of 29); combined Bright's and heart disease, 19 (out of 85); combined renal and other chronic diseases, 16 (out of 51).

The micro-organisms causing these infections, 38 in all, were the streptococcus pyogenes, 16 cases; staphylococcus pyogenes aureus, 4 cases; micrococcus lanceolatus, 6 cases; gas bacillus, three times alone and twice combined with the bacillus coli communis; the gonococcus, anthrax bacillus, bacillus proteus, the last combined with the bacillus coli, the bacillus coli alone, a peculiar capsulated bacillus, and an unidentified coccus, each in one instance.

What is striking in this list is the preponderance of the usual pyogenic cocci. These may occur without association with abscess formation. In a large proportion of our cases of septicæmia visible focal lesions within the organs were not present at the autopsy. The usual conditions found were acute splenic tumour and more or less severe parenchymatous degeneration of the viscera, with sometimes microscopical necroses of tissue cells as well.

No attempt has been made to separate the streptococci into distinct groups, and in this paper they are all included under the designa-

* Such a case was that of a young man who had a healed tuberculous lesion of the dorsal vertebræ associated with kyphosis. A general streptococcus infection, unsuspected during life, was found at the autopsy. No source of the infection was present on the surface of the body, in the serous cavities, or in the internal organs. Painstaking search revealed a small streptococcus abscess, embedded in the deep muscles of the back, in the region of the healed tuberculous focus. The heart of the individual was hypertrophied and dilated, the hypertrophy affecting chiefly the right side. The cavity of the thorax was small; the lungs the seat of chronic passive congestion. The myocardium was the seat of fatty degeneration.

tion of streptococcus pyogenes, notwithstanding certain cultural differences noted in the behaviour of specimens from different sources. For the most part the streptococci were not highly pathogenic for laboratory animals.

The characters of the staphylococcus aureus are so well marked that no trouble is found with its classification.

The micrococcus lanceolatus was identified from its morphological and cultural properties, as well as its well-known pathogenic effects upon animals.

Concerning the bacillus aerogenes capsulatus it may be said that there is evidence of the distribution of the bacilli within the body during life, although I am reluctant to admit a general invasion of the blood and tissues before death. The maintenance of life for any length of time after this organism has established itself in the blood and produced gas there is probably impossible.

The cases of proteus septicæmia are of their kind unique, and bear upon the growing belief that this group of bacteria may exhibit distinct pathogenic properties for man. The case of anthrax septicæmia is of interest, as it was associated with an acute endocarditis and peritonitis due to the bacillus anthracis.* Of more than ordinary interest is the case of gonococcus septicæmia with localization upon the heart valves.† A second instance of general infection with the gonococcus following gonorrhœa has just been noted by us. This case will be reported in full later by Drs. Thayer and Lazear.

In a few instances bacteria which could not be brought into harmony with any of the described pathogenic species were isolated, at one time from one or two organs, at another from a local inflammation, or, more rarely still, from several organs, or the heart's blood. These unidentified bacteria are reserved for a fuller description hereafter.

The portals of entry of the micro-organisms in these cases of general infection were in some instances made out and in others not. In some cases localized areas of inflammation existed which were taken

* Reported by Blumer and Young. *Johns Hopkins Hospital Bulletin*, 1895, Nos. 54, 55.

† Reported by Thayer and Blumer. *Ibid.*, 1896, No. 61.

to have antedated the general invasion. Not a few of these demand themselves an explanation of the point of entrance of the infectious agent.

Of the 16 instances of streptococcus infection the infection atria into the general circulation are believed to be as follows: Cellulitis, erysipelas, leg ulcer, bedsore, 7; phthisical cavity, 1; laparotomy, 2; tapping abdomen, 1; acute pleurisy, peritonitis, or pericarditis, 3; sloughing angio-sarcoma, 1; necrosis of placental attachment in uterus, 1.

Of the 4 cases of staphylococcus aureus septicæmia there were: Acute pericarditis following diphtheria, 1; operation upon the perinæum and cervix uteri, 2; undetermined (generalized melanotic sarcoma), 1.

Of the 6 cases of micrococcus lanceolatus infection, acute pneumonia claims 4; acute endocarditis and acute pericarditis, and pleuritis, 1 each.

The 5 gas-bacillus cases give aneurism of the aorta opening externally, amputation of arm, each 1 case, and intestine 3 cases.

The 2 proteus cases take their origin, one in a sloughing bedsore and the other from a chronic diphtheritic colitis.

The capsulated bacillus gained entrance from an ascending pyelonephritis; the anthrax bacillus from an anthrax œdema of the face.

The number of local infections is much larger. Of the cases of chronic Bright's disease alone, 26 occur in which bacteria were present in some local situation; of the cases of combined kidney and heart disease 66, and of kidney and other chronic diseases 35.

The micro-organisms found in the local situations are, for the most part, the same as were met with among the general infections. They are not infrequently associated with one another, and occasionally it happens that the different organs contain different bacteria. Indeed, certain bacteria appear with such uniformity within certain organs that these must be regarded as presenting better opportunities for their growth than do others. Examples are afforded by the colon bacillus which is so commonly found in the kidneys and the lungs, and the occurrence of streptococci in congested and œdematous lungs.

The following table exhibits the variety, combinations, and fre-

quency of occurrence of the micro-organisms found in the local infections:

	Times.
Streptococcus alone	14
Streptococcus and b. coli	15
Streptococcus and staphylococcus	2
Streptococcus and b. lactis aërogenes	1
Streptococcus and b. pyocyaneus	1
Streptococcus and unidentified bacilli	2
Staphylococcus aureus	8
Staphylococcus aureus and b. coli	3
Staphylococcus albus and b. coli	1
Streptococcus, staphylococcus aur., and b. coli	4
Streptococcus, staphylococcus aur., and b. lactis aërogenes	1
Micrococcus lanceolatus	12
Micrococcus lanceolatus and b. coli	3
Micrococcus lanceolatus, streptococcus, and staphylococcus	4
Micrococcus lanceolatus and streptococcus	1
Micrococcus lanceolatus and staphylococcus aureus	1
Micrococcus lanceolatus and b. aërogenes capsulatus	2
Bacillus coli communis	20
B. coli and b. diphtheriæ	1
B. coli, b. diphtheriæ and streptococcus	1
B. coli, streptoc., staphyl. alb., and unidentified bac.	1
B. pyocyaneus and b. coli	2
B. pyocyaneus and b. lactis aërogenes	1
B. pyocyaneus, m. lanceolatus, and b. coli	1
B. pyocyaneus and streptococcus	1
B. proteus	1
B. proteus and b. coli	1
B. proteus and b. pyocyaneus	1
B. aërogenes capsulatus	1
B. aërogenes capsulatus, b. coli, and staphylococcus	1
B. aërogenes capsulatus, b. coli, and streptococcus	1
B. influenzæ	2
B. diphtheriæ	1
Staphylococcus cereus flavus	2
B. tetani, streptoc., s. aureus, b. coli	1
Gonococcus, staphyl. alb., and streptococcus	1
Undetermined bacilli	3

Upon analyzing this group we find that at least one place of localization is found in the following situations with the frequency mentioned:

	Cases.
Acute peritonitis	37
Acute pleuritis (without pneumonia)	11
Acute pericarditis	23
Acute endocarditis	19
Acute meningitis	4

In reference to this group, it may be said that along with the micro-organisms in the foci of inflammation the same bacteria as are present there may appear in one or more of the organs of the body. Their distribution is, however, not so general as to warrant their classification among the true septicæmias.

The varieties of bacteria which are present in these situations is shown by the following summary, which also exhibits the portals of entry of the micro-organisms so far as they could be determined with some probability:

ACUTE PERITONITIS.

Bacteria.	Frequency.	Infection atrium.	
Streptococcus	8	Intestine	13 times.
Staphylococcus aureus and albus	9	Laparotomy	13 "
Micrococcus lanceolatus	4	Tapping abdomen	2 "
Bac. aërogenes capsulatus	2	Pneumonia	3 "
Bac. coli communis	3	Sloughing myoma uteri	2 "
Bac. pyocyaneus	1	Pyelonephritis	1 time.
Bac. proteus	1	Doubtful	3 times.
Bac. anthracis	1		
Staphylococcus cereus flavus	1		
Streptococcus and staphyl. aureus	2		
Streptococcus and b. coli	1		
Streptococcus, staphyl. aur., and b. coli	1		
Streptococcus, staphyl. alb., and undetermined bacilli	1		
Bac. pyocyaneus and b. coli	1		
Unidentified bacilli	1		

ACUTE PERICARDITIS.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	11	Pneumonia	8 times.
Streptococcus	4	Bronchitis	2 "
Staphylococcus aureus	1	Erysipelas	1 time.
Bac. pyocyaneus	1	Leg ulcer	1 "
Bac. influenzæ	1	Tonsils	1 "
M. lanceolatus and b. coli	1	Peritonæum	1 "
Streptococcus, staphyl. aur., and b. coli	1	Cancer stomach	1 "
Staphylococcus and b. coli	2	Sloughing myoma	1 "
Unidentified bacilli	1	Doubtful	7 times.

ACUTE ENDOCARDITIS.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	5	Pneumonia	4 times.
Streptococcus	7	Intestine	1 time.
Staphylococcus aureus	2	Ulcer leg	1 "
Bac. influenzæ	2	Sloughing carc. uterus	1 "
Streptococcus and staphylococcus	1	Abscess liver	1 "
Bac. pyocyaneus and b. coli	1	Carcinoma pylori	1 "
Undetermined	1	Doubtful	10 times.

Acute Pleurisy.

Bacteria.	Frequency.	Infection atrium.	
Streptococcus	4	Peritonæum	4 times.
Micrococcus lanceolatus	2	Intestine	3 "
B. coli com.	1	Bronchitis	1 time.
B. proteus	1	Infarction lung	1 "
Streptococcus, staphyl. aur., b. coli	1	Doubtful	2 times.
B. aërog. caps. and b. coli	1		
B. coli and unidentified bacillus	1		

Acute Meningitis.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	3	Ac. lobar pneumonia	3 times.

The intestine, as will appear from these statements, is regarded as the portal of entry not only of many of the bacteria found in the inflamed peritonæum, but also of some of those present in the pleura, upon the heart valves, and within the organs. This conclusion is based in part upon the behaviour of those species which are known to be derived from the intestine, namely, the colon group of bacilli. It has been found that these bacteria wander through the intestinal walls with great regularity where lesions of the intestinal mucosa exist. The lesions present here need not for this purpose be considerable, as localized areas of hyperæmia and small hæmorrhages often suffice to open the way for their escape; in grave lesions, such as necroses, ulcerations, and tumours, the colon bacilli are found almost without exception in some of the distant viscera. It is considered probable that the definitely pathogenic species of bacteria which are not infrequently associated with the colon bacilli in the intestine may find similar, although probably not identical, opportunities for escape.*

The occurrence of the colon bacilli in the organs is frequently unassociated with any lesion referable to their presence. Indeed, in the great majority of cases we have not looked upon the presence of a moderate number of colon bacilli as of pathological significance. In a few cases, however, they were present so generally in the body and in such large numbers that they could not be disregarded, and in rare instances they were found in association with definite lesions in such a manner as to leave no reasonable doubt of their pathogenic character.

* See Flexner, Peritonitis caused by the Invasion of the Micrococcus Lanceolatus from the Intestine. *Johns Hopkins Hospital Bulletin*, 1895, No. 49.

On the other hand, the frequent occurrence of the colon bacillus in combination with the pyogenic cocci is a matter of considerable importance, and, under such circumstances, these micro-organisms may come to have greater significance.

The majority of cases of acute pericarditis and acute endocarditis are found at the autopsy to be associated with pneumonia, either lobar or lobular in nature. As the micro-organisms present in the several lesions are usually the same, it is probable that the pneumonia is the source of the pericardial and endocardial infection. Cases of pleurisy associated with pneumonia have not been included in our list. In some instances acute pericardial and endocardial inflammations have been met with independently of pneumonia, and these may, indeed, be the sources from which other serous surfaces become infected, or a general infection arises.

In cases of heart disease uncomplicated with kidney disease, terminal infections are often encountered. Of 41 cases of arterio-sclerosis and chronic valvular disease, cultures showed in 32 the presence of bacterial infection, while in 22 cases of cardio-vascular disease, associated with some other chronic condition than Bright's disease, positive results were obtained in 16. In these 48 positive cases the distribution of the bacteria was general in 14 instances. The micro-organisms associated with these septicæmias were streptococcus pyogenes, 9 cases; micrococcus lanceolatus, 2 cases; staphylococcus pyogenes aureus, 1 case; staphylococcus albus and streptococcus, 1 case; bacillus coli communis, 1 case.

The portals of entry in the above cases are believed to have been as follows:

Streptococcus	Leg ulcer, ulcer scrotum, circumcision	3
	Laparotomy and peritonitis	1
	Abscess of back (kyphosis)	1
	Tonsil	1
	Carcinoma of stomach	1
	Sloughing carcinoma of neck	1
	Otitis media	1
	Doubtful	1
Staphylococcus aureus	Fracture of skull and acute meningitis.	
Micrococcus lanceolatus	Doubtful (no pneumonia).	
Bacillus coli communis	Intestine.	

The remaining 32 cases of infection were of local nature, and of this number 22 occurred in uncomplicated cardio-vascular disease, and 10 in combined chronic cardiac and other disease. As in the case of the summary of renal diseases, we find here also that the variety of infecting bacteria is greater than in the cases of general infection. The following gives the kind of bacteria and the frequency and manner of their occurrence:

Bacillus coli communis	4
Streptococcus pyogenes	4
Micrococcus lanceolatus	4
Bacillus lactis aërogenes	1
Bacillus pyocyaneus	1
Staphylococcus pyogenes aureus	2
Staphylococcus pyogenes aureus and bacillus coli	1
Staphylococcus pyogenes aureus, streptococcus, gas bacillus, and bacillus coli	1
Streptococcus and gas bacillus	1
Streptococcus and bac. fœtidus	1
Bacillus coli and liquefying bacillus (undetermined)	1
Undetermined bacilli	3

I would direct attention to the fact which must now be admitted, that the bacillus pyocyaneus which occurs several times in our tables is like the more common pyogenic organisms, capable of producing distinct and widespread lesions in human beings. We have met with several instances in which extensive necrosis, associated at times with ulceration, had been caused by it in the gastro-intestinal tract.

The special places of localization of the bacteria in the last series of cases is shown by the following summary:

Acute peritonitis	9
Acute pleuritis (without pneumonia)	6
Acute pericarditis	8
Acute endocarditis	15
Acute meningitis	3

The micro-organisms which were isolated from each of the above situations were the following:

Acute Peritonitis.

Bacteria.	Frequency.	Infection atrium.	
Streptococcus	5	Gastric ulcer	1 time.
Bacillus coli communis	3	Laparotomy	5 times.
Streptococcus and bac. fœtidus	1	Carcinoma stomach	1 time.
		Circumcision	1 "
		Doubtful	1 "

ACUTE PERICARDITIS.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	5	Pneumonia	2 times.
Streptococcus	1	Tonsil	1 time.
Bacillus coli	1	Bronchitis	1 "
Gonococcus	1	Peritonæum	1 "
		Urethra	1 "
		Doubtful	2 times.

ACUTE ENDOCARDITIS.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	7	Pneumonia	3 times.
Streptococcus	5	Pleurisy	1 time.
Gonococcus	1	Bronchitis	1 "
Streptococcus, staphylococcus aureus,		Tonsil	1 "
and b. influenza	1	Otitis media	1 "
Chain bacilli (unidentified)	1	Circumcision	1 "
		Urethra	1 "
		Acute endometritis	1 "
		Carcinoma uteri	1 "
		Doubtful	4 times

ACUTE PLEURISY.

Bacteria.	Frequency.	Infection atrium.	
Streptococcus	3	Bronchitis	1 time.
Micrococcus lanceolatus	2	Circumcision	1 "
Gonococcus	1	Urethra	1 "
		Doubtful	3 times.

ACUTE MENINGITIS.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	2	Pneumonia	1 time.
Streptococcus	1	Fracture of skull	1 "
		Operation on pharynx	1 "

This list leaves unmentioned a considerable number of cases in which, in the absence of micro-organisms in or inflammation of the serous cavities and upon the heart valves, pathogenic bacteria were found in one or several of the viscera. It would lead too far afield to consider the character of the lesions which may be associated with the invasion of the pathogenic bacteria which we have considered. But beside those which were at once evident to the naked eye, microscopic foci of cell degeneration and necrosis were frequently encountered.

The summary presented above will, if I mistake not, suffice to show the value of systematic bacteriological studies at human autopsies. It will also serve to emphasize the importance of the rôle played by pre-existing chronic disease in determining susceptibility to infec-

tion, and to illustrate the statement of Osler: "It may seem paradoxical, but there is truth in the statement, that persons rarely die of the disease with which they suffer. Secondary infection, or, as we are apt to call them in hospital wards, terminal infections, carry off many of the incurable cases in the wards." *

Now that the subject of the intoxications is coming to have so much significance in human pathology, and there is reason to believe that many of the bacterial infections do harm by intoxication rather than by infection, *per se*, it might be pertinent to ask how far the operation of toxic substances may be responsible for still other examples of death in chronic disease, and whether there exists under these circumstances greater vulnerability to the actions of these poisons just as we must admit a lessened resistance to the invasion of pathogenic bacteria.†

The exact factors concerned in producing the increased susceptibility to infection in chronic disease are quite unknown. That the lessened resistance depends upon profound alterations in the body constituents is certainly probable, and, in view of the disturbance of function associated with changes in organic structure, it is not difficult to form conjectures as to their possible character. We are also helped to a conclusion by the experiments upon animals, which tend to show that various injurious influences, by modifying the quantity and quality of the blood, the physiological nutrition and state of rest of the body, as well as its normal metabolism, increase susceptibility to infection.

It is exceedingly probable that pathogenic micro-organisms not infrequently gain entrance within the body in health, but do little harm there, and are quickly removed or destroyed. We have abun-

* Osler, Practice of Medicine, 1895, p. 132.

† Cf. Bouchard, Leçons sur les auto-intoxications dans les maladies. Paris, 1887. Roger, Action du foie sur les poisons. Paris, Thèse, 1887. Also Rôle du foie dans les auto-intoxications. *Gaz. des hôpitaux*, 1887, p. 66. Ewald u. Jacobson, Ueber ptomainartige Körper im Harn bei chronischen Krankheitsprocessen. *Berliner klin. Wochenschrift*, 1894, No. 2, p. 25. Albu, Ueber die Auto-intoxicationen der Intestinaltractus. Berlin, 1895. Kraus u. Honigmann, Pathologie der Auto-intoxicationen. *Ergebnisse der Allg. Pathologie u. Pathologischen Anatomie*, Zweite Abtheilung, 1895, p. 573.

dant evidence of the power of the body to destroy many pathogenic bacteria which enter it from without or are introduced by experiment, and thus the conclusion that in chronic disease the mechanisms of disposal of bacteria are in abeyance or insufficient is not to be resisted.

The chief defences against the invasion of pathogenic micro-organisms are the body fluids and cells. To this activity of the juices of the body and certain of its constituent cells is doubtless owing our relative immunity from living disease germs. It is therefore of the first importance to know whether under the conditions which have been shown to predispose to infection there is a demonstrable difference in the bactericidal power possessed by these substances.

The experiments which will be given here have been made with the blood-serum of a number of cases of chronic disease from the medical wards of the Johns Hopkins Hospital. I wish to express my indebtedness to Dr. Osler for his courtesy in placing these patients at my disposal, and to the house staff for their ready co-operation. For the purpose of comparison, blood obtained in surgical operations from healthy individuals was employed. For the placental blood I am indebted to Dr. Dobbin, the resident obstetrician, who collected it for me in sterile tubes immediately after cutting the umbilical cord.

The blood of adults was obtained directly from veins by aspiration.* A Roux syringe, sterilized by steam, was employed, the skin of the patient first having been scrupulously cleansed. This method is believed to have advantage over cupping as employed by Stern. Contaminations of the blood were never encountered, and 10 cubic centimetres, or even more, were readily secured at a single operation. The blood was immediately transferred to Nuttall's bulbs, as it was found that the serum separated better in these than in test tubes. After a period varying from two to thirty hours the serum was pipetted off into test tubes, 1 cubic centimetre being the standard amount used in each experiment.

* In two instances the blood was aspirated immediately after death from the heart, and in another instance from the femoral vein. In all cases only sterile blood was employed, cultures upon agar-agar being employed for this determination.

The bacteria which I have thus far tested upon human blood-serum are: (1) staphylococcus pyogenes aureus, (2) bacillus typhosus, (3) bacillus of Friedländer. The experiments are most complete as regards the first-mentioned micro-organism, and the present report will refer exclusively to it. The reasons which led to the selection of the staphylococcus aureus for the first series of experiments are the following: The study of the cases of terminal infections in human beings showed that the pyogenic cocci were the chief bacteria concerned with such infections. It was therefore considered most natural to expose these to the action of the serum. The staphylococcus aureus is not the chief invader in these infections; it is exceeded both by the streptococcus pyogenes and the micrococcus lanceolatus. However, the development upon culture media of the last two forms is subject to such variation under favourable conditions that the error of experiment must have been much greater than with the golden staphylococcus, which presents no such difficulties.

Writers do not entirely agree as to the effects of the normal fluids of the body upon the pyogenic cocci, the majority (Nuttall,* Stern,† Prudden ‡) stating that they are quite without effect. On the other hand, Rovighi # considers that he has shown human blood-serum to possess bactericidal properties for the staphylococcus aureus. He also observed a reduction of this power for the staphylococcus aureus in two out of six persons suffering from severe cachexia.

In our experiments the blood of a number of persons has been subjected to study, and from the results obtained it will appear that normal human blood-serum does possess distinct bactericidal properties for staphylococcus aureus; and also that this power is absent, or diminished, in at least some cases of advanced chronic disease.

Our experiments show that the destructive effect exerted by the normal blood-serum upon the staphylococcus aureus is not an invariable quantity, and is at most much less marked than is observed with

* *Zeitschrift für Hygiene*, 1885, Band iv, p. 353.

† *Zeitschrift für klin. Medicin.*, 1890, Band xviii, p. 46.

‡ *Medical Record*, 1890, vol. xxxvii, p. 85.

Atti della R. Accademia medica di Roma, Anno 16, vol. 5, Serie 11, Rom., 1890.

some other pathogenic bacteria, such as the bacteria of Asiatic cholera and of typhoid fever. It is, however, unjustifiable to compare, as has been done, the reduction in numbers which takes place when the golden staphylococcus is transplanted to blood-serum, with the diminution which regularly occurs after the introduction of the micro-organism into physiological salt solution. The two processes have little in common; the one fluid (blood-serum) is at first destructive, and, after spending its power in this direction, becomes a suitable culture medium, while the other (salt solution) permits at first a small increase of organisms from the nutriment carried over, and then leads in a relatively short time to a gradual, but often complete, disappearance from starvation of the added micro-organisms.

The method of determining the effect of the human serum was the one usually employed. It consisted in introducing a suspension of a young agar or potato culture of the staphylococcus aureus in physiological salt solution into the blood-serum. The same oese was used throughout each series of experiments, and care was exercised not to carry any of the nutritive material into the inoculated serum. Duplicate sets of plates were commonly employed. The inoculated blood-serum was kept at the temperature of 35.5° to 36° C. The agar-agar plates were permitted to develop for at least forty-eight hours at this temperature. For the enumeration of crowded plates the counter of Lafar * was used under a very low power (Ziess objective A_2, eye-piece No. 2) of the microscope. I also found this instrument very convenient for counting with the naked eye when a moderately large number of colonies had developed upon the plates. This method of estimation is not free from error; but when carefully conducted the duplicate counts are in remarkable accordance with each other.

Action of Normal Human Serum upon Staphylococcus Aureus.

No.	Control plate.	1 hour.	2 hours.	4 hours.	6 hours.	24 hours.
1	33,764	.....	.....	4,823	11,255	Increase.
2	25,272	.....	18,925	8,424	4,212	Increase.
3 †	10,920	7,800	7,210	5,740	.....	Increase.

* *Zeitschrift für Nahrungsmittel-untersuchung.*, Wien., 1893, No. 24, p. 429. (Abst. *Centralbl. f. Bakteriologie u. Parasitenkunde*, 1894, Band xv, p. 331.)

† Blood from the enlarged veins in a myoma of the uterus.

Action of Placental Blood-serum upon Staphylococcus Aureus.

No.	Control plate.	2 hours.	3 hours.	4 hours.	6 hours.	24 hours.
1	33,260	34,590	.....	39,912	.....	Increase.
2	73,632	67,494	.....	77,511	156,000	Increase.
3	46,566	.....	.....	56,000	200,000	Increase.
4	210,432	.....	.....	280,000	.....	Increase.

Action of Human Serum from Cases of Chronic Diseases upon Staphylococcus Aureus.

No.	Control plate.	1 to 2 hours.	3 to 4 hours.	6 hours.	8 hours.	24 hours.
1*	33,764	.....	28,137	.....	4,220,500	Increase.
2†	57,720	52,000	.....	Increase.	.....	Increase.
3‡	20,614	17,179	30,000	75,000	.....	Increase.
4#	11,154	13,013	.....	.....	50,193	Increase.
5‖	50,000	.....	63,000	.....	.....	Increase.
6△	62,400	51,434	.....	100,000	.....	Increase.
7◊	26,676	15,246	.....	10,166	6,356	Increase.
8‡	66,456	32,000	.....	16,000	.....	Increase.
9↕	14,742	9,828	952	.....	.....	Increase.

* Arterio-sclerosis; mitral insufficiency; failure of compensation.
† Arterio-sclerosis; chronic nephritis.
‡ Arterio-sclerosis; multiple aneurism formation; chronic nephritis.
# Aortic insufficiency.
‖ Chronic nephritis; uræmia.
△ Chronic nephritis; general anasarca.
◊ Arterio-sclerosis; aortic insufficiency. (Discharged improved.)
‡ Emphysema; heart hypertrophy. (Discharged improved after bloodletting.)
↕ Aortic and mitral insufficiency.

The foregoing tables show that of three specimens of average normal human blood-serum one only did not possess marked destructive power for the staphylococcus aureus, and with respect to this sample it may be questioned whether it is to be regarded as strictly belonging to this class.* The greatest number of micro-organisms destroyed was 29,000 in four hours (Case I), and 21,000 in six hours (Case II). Of nine samples of blood taken from persons suffering with some form of chronic disease, in six no appreciable effect was exerted upon this micro-organism. Regarding the three samples in which more or less bactericidal effect was produced, it is of interest to record that in two (No. 7 and 8) the patients improved while in the hospital, and in one instance only (No. 9), in which the blood-serum exhibited distinct bac-

* The figures given in the first table may be taken as representative, as several subsequent estimations confirm them. In one case only (convalescent from measles) was this power missed in normal adult human serum.

tericidal effects, did the patient die within a short time of the examination. It is not a little surprising, in view of the other results given, to find that placental blood-serum exerts at most a temporary inhibition of development of this organism. On the other hand, the placental serum showed marked destructive power for the bacillus typhosus.

Time does not permit a detailed consideration of the relation of immunity to the bactericidal property of the blood-serum, and, indeed, it is admitted that there is no fixed relation between these phenomena. Yet observations are not wanting to show that in both natural and acquired immunity a correspondence between this property of the blood-serum or its absence exists; however, not in all cases. The serum of the rat is destructive to anthrax bacilli, while that of man and the mouse have little or no effect upon these micro-organisms, and the serum of the rabbit varies in its behaviour. Similarly the blood-serum of the immune guinea-pig, when diluted with bouillon, exerts injurious effects upon the cholera vibrio, which the normal serum fails to do.* The serum, too, of the vaccinated calf destroys the activity of the vaccine virus, while the ordinary serum leaves it unaffected.† There is much significance, too, in the observation that just those micro-organisms which are readily and quickly killed by the serum are rarely or never found in the circulating blood in their respective diseases. Examples of this are furnished by Asiatic cholera and typhoid fever. Further, Flügge has pointed out that in anthrax infection in rabbits the bactericidal effect of the blood is lost before the bacilli make their way into the larger vessels.

Normal blood-serum contains, in addition to bactericidal principles, antitoxic substances which must be of great importance in establishing and preserving immunity.‡ The comparative study of the antitoxic values of blood derived from persons suffering from chronic disease is reserved for a later communication.

* Pfeiffer, *Deutsche med. Wochenschrift*, February 13, 1896.

† Sternberg, Immunity and Serum Therapy, New York, 1895, p. 234.

‡ Escherich u. Klemensiewicz, *Centralbl. für Bakteriologie*, 1893, Band 13, p. 153. Abel, *Deutsche med. Wochenschrift*,, 1894, Nos. 48 u. 50, p. 899 u. 936. Wassermann, *Zeitschrift für Hygiene*, 1895, Band 19, p. 408. Fischl u. v. Wunschheim, *Zeitschrift für Heilkunde*, 1895, Band 16, p. 429.